

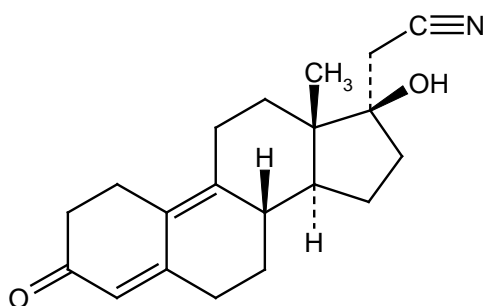
## PRODUCT INFORMATION

### VALETTE®

#### NAME OF THE MEDICINE

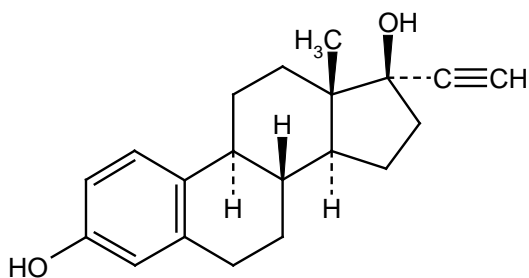
VALETTE is a combined oral contraceptive (COC) preparation containing the synthetic progestogen, dienogest and the synthetic estrogen, ethinylestradiol as the active substances.

Dienogest is a progestogen. The chemical name for dienogest is 17 $\alpha$ -cyanomethyl-17 $\beta$ -hydroxy-estra-4,9(10)-dien-3-one and has the following structural formula:



Chemical formula:	C <sub>20</sub> H <sub>25</sub> NO <sub>2</sub>
Molecular weight:	311.42
Melting point:	210-218°C
CAS No.:	65928-58-7

Ethinylestradiol is an estrogen. Chemically, ethinylestradiol is 19-nor-17 $\alpha$ -pregna-1,3,5(10)-trien-20-yne-3, 17 $\beta$ -diol and has the following structural formula:



Chemical formula:	C <sub>20</sub> H <sub>24</sub> O <sub>2</sub>
Molecular weight:	296.41
Melting point:	181-185°C
CAS No.:	57-63-6

## DESCRIPTION

Dienogest is a white to pale yellow crystalline powder: odourless; practically insoluble in water, sparingly soluble in ethanol and acetone, soluble in chloroform.

Ethinylestradiol is a white to creamy white, odourless, crystalline powder. It is insoluble in water and soluble in alcohol, chloroform, ether, vegetable oils, and aqueous solutions of alkali hydroxides.

Each small white active tablet contains dienogest 2 mg, ethinylestradiol 30 µg and the excipients: lactose monohydrate, maize starch, magnesium stearate, sucrose, liquid glucose, calcium carbonate, povidone, macrogol 35000, carnauba wax, maltodextrin and titanium dioxide.

Each brown inactive tablet contains lactose monohydrate, maize starch, purified talc, magnesium stearate, povidone, sucrose, macrogol 6000, calcium carbonate, titanium dioxide, glycerol, ferric oxide, glycol montanate.

## PHARMACOLOGY

### Pharmacodynamic properties

The contraceptive effect of combined oral contraceptives (COCs) is based on the interaction of various factors. The primary mechanisms are inhibition of ovulation (by suppression of gonadotrophins) and changes in the cervical secretion (blocking the entry of sperm into the uterus). As well as protection against pregnancy, combined oral contraceptives have several positive properties which, next to the negative properties (see PRECAUTIONS, ADVERSE EFFECTS), can be useful in deciding on the method of birth control. For the majority of users, the cycle is more regular, the menstruation is often less painful and bleeding is lighter. The latter may result in a decrease in the occurrence of iron deficiency.

Dienogest has beneficial properties in addition to contraception. Dienogest exerts antiandrogenic activity leading to a positive effect on the skin and to a reduction in acne lesions and sebum production. In addition, with the higher-dosed COCs (50 µg ethinylestradiol), there is evidence of a reduced risk of fibrocystic tumours of the breasts, ovarian cysts, pelvic inflammatory disease, ectopic pregnancy and endometrial and ovarian cancer. Whether this also applies to lower-dosed combined oral contraceptives such as VALETTE remains to be confirmed.

### Pharmacokinetic properties

Bioavailability studies have been conducted with VALETTE.

- **Dienogest**

#### Absorption

After single oral administration of 2 mg dienogest in combination with 30 µg ethinylestradiol, dienogest is absorbed rapidly and almost completely. Maximum plasma concentrations of  $51.6 \pm 9.5$  ng/mL are reached in  $2.4 \pm 1.4$  hours after single dose oral administration. A high absolute bioavailability of about 96% was demonstrated in a bioavailability study.

### Distribution

10% is present in plasma in free form, whilst approx. 90% is bound non-specifically to albumin. Unlike all other 19-norprogesterones, dienogest does not bind to the specific transport proteins, sex hormone-binding globulin (SHBG) and corticosteroid-binding globulin (CBG). As there is therefore no possibility of testosterone being displaced from its SHBG binding or of cortisol being displaced from its CBG binding, an influence on the physiological transport processes for endogenous steroids is unlikely.

The half-life of dienogest is  $9.3 \pm 1.8$  hours, which is relatively short compared to other progestogens. There is thus very little accumulation with daily administration.

### Metabolism

Dienogest is metabolised mainly by hydroxylation but also by hydrogenation, conjugation and aromatisation, to endocrinologically largely inactive metabolites. The contribution of the metabolites to the pharmacological and toxicological effects of dienogest is insignificant.

### Elimination

After an oral dose of 0.1 mg/kg body weight, the ratio of renal to faecal excretion is 3.2. The total clearance is  $3.66 \pm 0.71$  L/h after a single dose.

### Steady state conditions

The pharmacokinetics of dienogest is not influenced by SHBG levels. Following daily ingestion, drug serum levels increase about 1.5 fold reaching steady state conditions after approximately 4 daily administrations.

## • **Ethinylestradiol**

### Absorption

Orally administered ethinylestradiol is absorbed rapidly in the small intestine. 50-60% of it is converted primarily to sulphate metabolites in the wall of the small intestine and in the liver (first-pass effect). After administration of the ethinylestradiol-dienogest combination, the absolute bioavailability of ethinylestradiol is about 44%.

After a single administration of 30 µg ethinylestradiol and 2 mg dienogest, maximum plasma concentrations are reached after 1.5 to 4 hours.

### Distribution

Serum ethinylestradiol levels decrease in two phases, with an elimination half-life of  $11.7 \pm 6.5$  hours following single administration of 30 µg ethinylestradiol and 2 mg dienogest. Ethinylestradiol is highly but non-specifically bound to serum albumin (approximately 98.5 %), and induces an increase in the serum concentrations of SHBG.

### Metabolism

Ethinylestradiol is subject to presystemic conjugation in both small bowel mucosa and the liver. Ethinylestradiol is primarily metabolised by aromatic hydroxylation but a wide variety of hydroxylated and methylated metabolites are formed. These are present as free metabolites and as conjugates with glucuronides and sulphate. The metabolic clearance rate of ethinylestradiol is about 5 mL/min/kg.

### Elimination

Ethinylestradiol is not excreted in unchanged form to any significant extent. The metabolites of ethinylestradiol are excreted 30-50% via the kidneys, with 30-40% being excreted with the faeces.

### Steady state conditions

Steady state conditions are reached during the second half of treatment cycle when serum drug levels are approximately two fold higher than that of a single dose of ethinylestradiol.

## **CLINICAL TRIALS**

The contraceptive efficacy and safety of VALETTE was examined in two open phase III multicentre studies, the first of which involved 2,290 evaluable women over a period ranging from 1 to 22 cycles, with 1,612 women completing 12 cycles. The second study investigated 97 women up to 12 cycles. The total cycle numbers were 28,183 and 686 respectively. The unadjusted Pearl Index for the first study was 0.68; the adjusted Pearl index was 0.21. No pregnancies occurred in the second study. Data are also available from two large post-marketing surveillance studies involving 92,146 treatment cycles from 16,087 women and 63474 treatment cycles in 10,718 women. In the first of these studies only 17 pregnancies occurred, 6 after discontinuation. The Pearl index was therefore 0.14. During the second study only 3 unintended pregnancies occurred, corresponding to an unadjusted Pearl Index of 0.057.

The effects on cycle control displayed in the phase III trials were as expected for a low dose combined oral contraceptive preparation. Intermenstrual bleeding was highest in the first cycle, with cycle stabilisation occurring with treatment duration. In the largest study spotting and breakthrough bleeding had been reduced by 50% after one year of treatment (from 21.5% in cycle 1 to 6.8% by cycle 12). The duration of bleeding decreased over the study periods, from 4.7 days to 3.2 days and from 6.2 days to 4 days in the two studies. Dysmenorrhoea, which occurred frequently before treatment (approx. 29%) had decreased so that 93% of women were complaint free by cycle 6 and it occurred only rarely after 12 cycles. Bleeding intensity also decreased under treatment. Prior to treatment 17.4% reported scanty bleeding and 7.4% excessive bleeding. By the 6th cycle 47.2% had scanty, and only 2% excessive bleeding.

Acne: A Phase III study (Clinical Research Report No. 28501) investigated the anti-acne effects of VALETTE versus both a placebo control arm and a comparator arm with Diane-35 (ethinylestradiol and cyproterone acetate). The primary efficacy variables were the percentage change from baseline to cycle 6 in inflammatory (papules, pustules, nodules) lesion count, the total lesion count and improvement in facial acne according to the investigator's global assessment (IGA). The hypothesis that VALETTE is superior to placebo and not inferior to Diane<sup>®</sup>-35 would only be correct if all 3 variables met the criteria. The study included 525 women treated with VALETTE, 537 with Diane-35 and 246 with placebo over 6 treatment cycles of 28 days. During the study, subjects were required to refrain from other anti-acne treatments and acne causing medications and comedogenic preparations. The results for the primary efficacy variables (FAS – Full Analysis Set) are provided in the Table below:

VARIABLE		VALETTE	PLACEBO	DIANE-35
<b>Percent change in total lesion count</b>		- 54.66	- 39.42	- 53.56
	SD	26.34	33.58	27.49
	N	515	259	528
<b>Percent changes in inflammatory lesion count</b>		- 65.60%	- 49.47%	- 64.56%
	SD	29.89	41.04	31.17
	N	511	257	526
<b>Number &amp; Percent of patients with improvement in facial acne according to IGA</b>		477 (91.9%)	199 (76.2%)	480 (90.2%)

The conclusion is that VALETTE is superior to placebo while similar results for all three variables were obtained for the VALETTE and Diane-35 groups leading to the conclusion that VALETTE is not inferior to Diane-35.

## INDICATIONS

VALETTE is indicated for use as an oral contraceptive and in the treatment of mild to moderate acne in women who seek oral contraception.

## CONTRAINDICATIONS

Combined oral contraceptive (COCs) including VALETTE, should not be used in the presence of any of the conditions listed below. Should any of the conditions appear for the first time during COC use, the product should be stopped immediately.

- Presence or risk of venous thromboembolism (VTE) (see PRECAUTIONS)
  - Current VTE (on anticoagulants) or history of deep venous thrombosis [DVT] or pulmonary embolism [PE]
  - Known hereditary or acquired predisposition for venous thromboembolism, such as APC-resistance (including Factor V Leiden), antithrombin-III-deficiency, protein C deficiency, protein S deficiency
  - Major surgery with prolonged immobilisation
  - A high risk of venous thromboembolism due to the presence of multiple risk factors
- Presence or risk of arterial thromboembolism (ATE) (see PRECAUTIONS)
  - Current ATE or history of ATE (e.g. myocardial infarction or stroke) or prodromal condition (e.g. angina pectoris or transient ischaemic attack [TIA])
  - Known hereditary or acquired predisposition for arterial thromboembolism, such as hyperhomocysteinaemia and antiphospholipid-antibodies (eg. anticardiolipin-antibodies and lupus anticoagulant)
  - History of migraine with focal neurological symptoms
  - A high risk of arterial thromboembolism due to multiple risk factors or to the presence of one serious risk factor such as:
    - diabetes mellitus with vascular symptoms
    - severe hypertension
    - severe dyslipoproteinaemia
- Pancreatitis or a history thereof if associated with severe hypertriglyceridemia

- Presence or history of severe hepatic disease as long as liver function values have not returned to normal
- Use of direct-acting antiviral (DAA) medicinal products containing ombitasvir, paritaprevir or dasabuvir and combinations of these (see INTERACTIONS WITH OTHER MEDICINES)
- Presence or history of liver tumours (benign or malignant)
- Known or suspected sex-steroid influenced malignancies (e.g. of the genital organs or the breasts)
- Undiagnosed vaginal bleeding
- Known or suspected pregnancy
- Hypersensitivity to any of the ingredients contained in VALETTE

## **PRECAUTIONS**

If any of the conditions/risk factors mentioned below are present, the benefits of VALETTE use should be weighed against the possible risks for each individual woman and discussed with the woman before she decides to start taking it. In the event of aggravation, exacerbation or first appearance of any of these conditions or risk factors, the woman should contact her doctor. The doctor should then decide on whether VALETTE use should be discontinued.

### **Circulatory disorders**

Epidemiological studies have suggested an association between the use of combined oral contraceptives (COCs) containing ethinyloestradiol and an increased risk of arterial and venous thrombotic and thromboembolic diseases such as myocardial infarction, stroke, deep venous thrombosis and pulmonary embolism. These events occur rarely in average-risk women.

### **Risk of venous thromboembolism (VTE)**

The use of any combined hormonal contraceptive (CHC) increases the risk of VTE compared with no use. The woman should be advised that her VTE risk is highest in the first ever year of use and that there is some evidence that the risk is increased when a CHC is re-started after a break in use of 4 weeks or more

Data from a large, prospective 3-armed cohort study<sup>1</sup> suggest that this increased risk is mainly present during the first 3 months.

A recently conducted, large (approximately 140,000 women years (WY) of observation), prospective, multinational, cohort study on the safety of OC use, the EURAS study<sup>1</sup> found that the VTE incidence in women with or without other risk factors for VTE who used COCs was in the range of 8-9.9 VTE per 10,000 WY. The study did not analyse incidence of VTE in VALETTE users separately.

The overall incidence rate for past OC users was 4.7 VTE/10,000 WY, which was further specified to 19.4 VTE/10,000 WY for pregnant past OC users and 2.3 VTE/10,000 WY for non pregnant past OC users.

Another recently conducted large population based study<sup>2</sup> found an incidence rate of 20 VTE/10,000 WY in pregnant or postpartal women and 4.6 in non pregnant women of reproductive age. These rates tend to be higher than those reported in the past.

Based on the new data it can be assumed that the VTE risk in OC users is roughly twice as high as for non pregnant non OC users. The absolute attributable risk (approximately 4 VTEs per 10,000 WY of use) was found to be slightly higher in these studies than reported in the past. Nevertheless the risk in OC users remains lower than the VTE risk associated with pregnancy and the first weeks following delivery.

It is important that women understand that VTE associated with CHC use is rare in average-risk women. The risk in pregnancy (5-20 per 10,000 women over 9 months) and the risk in the post-partum period (45-65 per 10,000 women over 12 weeks) is higher than that as associated with CHC use.

An additional increase in VTE risk for CHCs containing  $\geq 50 \mu\text{g}$  ethinylloestradiol cannot be excluded.

The decision to use any product other than one with the lowest VTE risk should be taken only after a discussion with the woman to ensure she understands the risk of VTE with CHCs, and how her current risk factors influence this risk.

The increased risk of VTE during the postpartum period must be considered if re-starting VALETTE (See DOSAGE AND ADMINISTRATION, Use in pregnancy and Use in lactation).

VTE may be life-threatening or may have a fatal outcome (in 1-2% of cases).

Extremely rarely, thrombosis has been reported to occur in CHC users in other blood vessels, e.g. hepatic, mesenteric, renal, cerebral or retinal veins and arteries.

The risk for venous thromboembolic complications in CHC users may increase substantially in a woman with additional risk factors, particularly if there are multiple risk factors (see list below).

VALETTE is contraindicated if a woman has multiple risk factors that put her at high risk of venous thrombosis. If a woman has more than one risk factor, it is possible that the increase in risk is greater than the sum of the individual factors – in this case her total risk of VTE should be considered. If the balance of benefits and risks is considered to be negative a CHC should not be prescribed.

When considering risk/benefit, the doctor should take into account that the adequate treatment of a condition may reduce the associated risk of thrombosis.

### ***Risk factors for VTE***

- Obesity (body mass index over 30 kg/m<sup>2</sup>). Risk increases substantially as BMI rises
- Prolonged immobilisation, major surgery, any surgery to the legs or pelvis, neurosurgery, or major trauma
- Temporary immobilisation including air travel >4 hours can also be a risk factor for VTE, particularly in women with other risk factors
- Positive family history (venous thromboembolism ever in a sibling or parent especially at a relatively early age e.g. before 50)
- Biochemical factors that may be indicative of hereditary or acquired predisposition for VTE include Activated Protein C (APC) resistance (including Factor V Leiden), antithrombin-III deficiency, protein C deficiency, protein S deficiency
- Other medical conditions associated with VTE include:
  - Cancer
  - Systemic lupus erythematosus

- Haemolytic uraemic syndrome
- Chronic inflammatory bowel disease (e.g. Crohn's disease or ulcerative colitis)
- Sickle cell disease
- Increasing age, particularly above 35 years
- Smoking

In women at risk of prolonged immobilisation (including major surgery, any surgery to the legs or pelvis, neurosurgery, or major trauma), it is advisable to discontinue use of VALETTE (in the case of elective surgery at least four weeks in advance) and not resume until two weeks after complete remobilisation. Another method of contraception should be used to avoid unintentional pregnancy. Antithrombotic treatment should be considered if VALETTE has not been discontinued in advance.

If a hereditary predisposition to VTE is suspected, the woman should be referred to a specialist for advice before deciding about any CHC use.

There is no consensus about the possible role of varicose veins and superficial thrombophlebitis in venous thromboembolism.

### ***Symptoms of VTE (deep vein thrombosis and pulmonary embolism)***

Women should be informed of the symptoms of VTE and be advised to seek urgent medical attention if VTE symptoms develop and to inform the healthcare professional that she is taking a CHC.

Symptoms of deep vein thrombosis (DVT) can include:

- unilateral swelling of the leg and/or foot or along a vein in the leg
- pain or tenderness in the leg which may be felt only when standing or walking
- increased warmth in the affected leg; red or discoloured skin on the leg

Symptoms of pulmonary embolism (PE) can include:

- sudden onset of unexplained shortness of breath or rapid breathing
- sudden coughing which may be associated with haemoptysis
- sharp chest pain or sudden severe pain in the chest which may increase with deep breathing
- severe light headedness or dizziness
- rapid or irregular heartbeat

Some of these symptoms (e.g. "shortness of breath", "coughing") are non-specific and might be misinterpreted as more common or less severe events (e.g. respiratory tract infections).

Other signs of vascular occlusion can include: sudden pain, swelling and slight blue discoloration of an extremity.

If the occlusion occurs in the eye symptoms can range from painless blurring of vision which can progress to loss of vision. Sometimes loss of vision can occur almost immediately.

### **Risk of arterial thromboembolism (ATE)**

Epidemiological studies have associated the use of CHCs with an increased risk for arterial thromboembolism (e.g. myocardial infarction, angina pectoris, stroke or TIA).



Arterial thromboembolic events may be fatal.

The risk of arterial thromboembolic complications in CHC users increases in women with risk factors. VALETTE is contraindicated if a woman has one serious or multiple risk factors for ATE that puts her at high risk of arterial thrombosis. If a woman has more than one risk factor, it is possible that the increase in risk is greater than the sum of the individual factors - in this case her total risk should be considered. If the balance of benefits and risks is considered to be negative a CHC should not be prescribed.

### ***Risk factors for ATE***

- Increasing age, particularly above 35 years
- Smoking
- Hypertension
- Obesity
- Positive family history (arterial thromboembolism ever in a sibling or parent especially at relatively early age e.g. below 50)
- Biochemical factors that may be indicative of hereditary or acquired predisposition for ATE include: hyperhomocysteinaemia and antiphospholipid antibodies (e.g. anticardiolipin antibodies, and lupus anticoagulant)
- Migraine
- Other medical conditions associated with adverse vascular events:
  - Diabetes mellitus
  - Hyperhomocysteinaemia
  - Valvular heart disease
  - Atrial fibrillation
  - Dyslipoproteinaemia
  - Systemic lupus erythematosus

Women should be advised not to smoke if they wish to use a CHC. Women over 35 years who continue to smoke should be strongly advised to use a different method of contraception.

If a hereditary predisposition is suspected, the woman should be referred to a specialist for advice before deciding about any CHC use.

An increase in frequency or severity of migraine during CHC use (which may be prodromal of a cerebrovascular event) may be a reason for immediate discontinuation.

### ***Symptoms of ATE***

Women should be informed of the symptoms of ATE and be advised to seek urgent medical attention if ATE symptoms develop and to inform the healthcare professional that she is taking a CHC.

Symptoms of a stroke can include:

- sudden numbness or weakness of the face, arm or leg, especially on one side of the body
- sudden trouble walking, dizziness, loss of balance or coordination
- sudden confusion, slurred speech or aphasia
- sudden partial or complete loss of vision; diplopia
- sudden, severe or prolonged headache with no known cause

- loss of consciousness or fainting with or without seizure

Temporary symptoms suggest the event is a transient ischaemic attack (TIA).

Symptoms of myocardial infarction can include:

- pain, discomfort, pressure, heaviness, sensation of squeezing or fullness in the chest arm, or below the breastbone
- discomfort radiating to the back, jaw, throat, arm, stomach
- feeling of being full, having indigestion or choking
- sweating, nausea, vomiting or dizziness
- extreme weakness, anxiety, or shortness of breath
- rapid or irregular heartbeats

## **Tumours**

The most important risk factor for cervical cancer is persistent human papilloma virus (HPV) infection. Some epidemiological studies have indicated that long-term use of COCs may further contribute to this increased risk but there continues to be controversy about the extent to which this finding is attributable to confounding effects, e.g., cervical screening and sexual behaviour including use of barrier contraceptives.

A meta-analysis from 54 epidemiological studies reported that there is a slightly increased relative risk (RR = 1.24) of having breast cancer diagnosed in women who are currently taking COCs. The excess risk gradually disappears during the course of the 10 years after cessation of COC use. Because breast cancer is rare in women under 40 years of age, the excess number of breast cancer diagnoses in current and recent COC users is small in relation to the overall risk of breast cancer. These studies do not provide evidence for causation. The observed pattern of increased risk may be due to an earlier diagnosis of breast cancer in COC users, the biological effects of COCs or a combination of both. The breast cancers diagnosed in ever-users tend to be less advanced clinically than the cancers diagnosed in never-users.

In rare cases, benign liver tumours, and even more rarely, malignant liver tumours have been reported in users of COCs. In isolated cases, these tumours have led to life-threatening intra-abdominal haemorrhages. A liver tumour should be considered in the differential diagnosis when severe upper abdominal pain, liver enlargement or signs of intra-abdominal haemorrhage occur in women taking COCs.

Malignancies may be life-threatening or may have fatal outcome.

## **Other conditions**

Women with hypertriglyceridaemia, or a family history thereof, may be at an increased risk of pancreatitis when taking COCs.

Although small increases in blood pressure have been reported in many women taking COCs, clinically relevant increases are rare. However, if a sustained clinically significant hypertension develops during the use of a COC, it is prudent for the physician to withdraw the COC and treat the hypertension. Where considered appropriate, COC use may be resumed if normotensive values can be achieved with antihypertensive therapy.

The following conditions have been reported to occur or deteriorate with both pregnancy and COC use, but the evidence of an association with COC use is inconclusive: jaundice

and/or pruritus related to cholestasis; gallstone formation; porphyria; systemic lupus erythematosus; haemolytic uraemic syndrome; Sydenham's chorea; herpes gestationis; otosclerosis-related hearing loss.

In women with hereditary angioedema exogenous estrogens may induce or exacerbate symptoms of angioedema.

Acute or chronic disturbances of liver function may necessitate the discontinuation of COC use until markers of liver function return to normal. Recurrence of cholestatic jaundice which occurred first during pregnancy or previous use of sex steroids necessitates the discontinuation of COCs.

Although COCs may have an effect on peripheral insulin resistance and glucose tolerance, there is no evidence for a need to alter the therapeutic regimen in women with diabetes taking low dose COCs (containing < 50 µg ethinylestradiol). However, women with diabetes should be carefully observed while taking COCs.

Crohn's disease and ulcerative colitis have been associated with COC use.

Chloasma may occasionally occur, especially in women with a history of chloasma gravidarum. Women with a tendency to chloasma should avoid exposure to the sun or ultraviolet radiation whilst taking COCs.

Each white active tablet contains 28.72 mg of lactose monohydrate and each brown placebo tablet contains 48.25 mg of lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption who are on a lactose free diet should take this amount into consideration.

### **Medical examination/consultation**

A complete medical history and physical examination should be taken prior to the initiation or reinstatement of COC use, guided by the contraindications and warnings, and should be repeated periodically during the use of COCs. In general, an annual examination is recommended. Periodic medical assessment is also of importance because contraindications (e.g. a transient ischaemic attack, etc.) or risk factors (e.g. a family history of venous or arterial thrombosis) may appear for the first time during the use of a COC. The frequency and nature of these assessments should be adapted to the individual woman but should generally include special reference to blood pressure, breasts, abdomen and pelvic organs, including cervical cytology, and relevant laboratory tests.

### **Sexually transmitted infections (STIs) including Human Immunodeficiency Virus (HIV) infections and AIDS**

VALETTE is intended to prevent pregnancy. It does not protect against STIs including HIV infections (AIDS). The woman should be advised that additional barrier contraceptive measures are needed to prevent transmission of STIs.

### **Reduced efficacy**

The efficacy of COCs may be reduced in the event of missed tablets (see DOSAGE AND ADMINISTRATION – Management of missed tablets), vomiting, diarrhoea (see DOSAGE AND ADMINISTRATION – Advice in case of gastrointestinal disturbances) or concomitant medication (see INTERACTIONS WITH OTHER MEDICINES).

## Reduced cycle control

With all COCs, irregular bleeding (spotting or breakthrough bleeding) may occur, especially during the first months of use. Therefore, the evaluation of any irregular bleeding is only meaningful after an adaptation interval of about three cycles.

If bleeding irregularities persist or occur after previously regular cycles, then non-hormonal causes should be considered and adequate diagnostic measures are indicated to exclude malignancy or pregnancy. These may include curettage.

In some women withdrawal bleeding may not occur during the placebo tablet interval. If the COC has been taken according to the directions, it is unlikely that the woman is pregnant. However, if the COC has not been taken according to these directions prior to the first missed withdrawal bleed or if two withdrawal bleeds are missed, pregnancy must be ruled out before COC use is continued.

## Use in pregnancy

Pregnancy Category B3<sup>1</sup>

The reproductive toxicity of VALETTE has not been assessed in animals. Oral treatment of rats or rabbits with dienogest (the progestogen component) during organogenesis caused up to 12% increase in post-implantation loss at systemic exposure levels (based on AUC) similar to that anticipated clinically. No teratogenicity was evident in either species at systemic exposure levels up to ten-fold higher than that expected in humans at the clinical dose, based on AUC.

Extensive epidemiological studies have revealed neither an increased risk of birth defects in children born to women who used COCs prior to pregnancy, nor a teratogenic effect when COCs were taken inadvertently during early pregnancy.

VALETTE is contraindicated during pregnancy. Pregnancy should be ruled out before the start of therapy. Should pregnancy occur during the use of VALETTE, VALETTE must be discontinued immediately.

## Use in lactation

Dienogest is excreted into rat milk. Impaired reproductive function was seen in female rat pups of dams administered dienogest in the peri/postnatal period at a systemic exposure level approximately one-third of that anticipated clinically, based on AUC. Based on animal data, there is some concern for an infant exposed to dienogest.

Lactation may be influenced by COCs as they may reduce the quantity and change the composition of breast milk. Small amounts of the contraceptive steroids and/or metabolites may be excreted with the milk. Therefore, the use of COCs should generally not be recommended until the nursing mother has completely weaned her child.

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<sup>1</sup> **Category B3**

Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals have shown evidence of an increased occurrence of fetal damage, the significance of which is considered uncertain in humans.

## **Paediatric use**

VALETTE is only indicated after menarche.

## **Use in the elderly**

VALETTE is not indicated after menopause.

## **Patients with hepatic impairment**

VALETTE is contraindicated in women with severe hepatic diseases whilst liver function values have not returned to normal.

## **Patients with renal impairment**

VALETTE has not been specifically studied in renally impaired patients.

## **Genotoxicity**

There is limited evidence available in the literature suggesting that estrogens may be weakly genotoxic at high doses. Ethinylestradiol was negative in studies for DNA-adduct formation in cultured human liver slices and in assays for gene mutations (bacterial or mammalian cells in vitro) and gave equivocal results in assays for chromosomal damage (clastogenic effects were not consistently seen and occurred at high doses).

Assays for gene mutations in bacteria and mammalian cells, clastogenicity both in vitro and in vivo and unscheduled DNA synthesis, did not provide any evidence of a genotoxic potential for dienogest.

## **Carcinogenicity**

No long-term animal studies of the carcinogenic potential of VALETTE have been performed. However, studies have been performed for both ethinylestradiol and dienogest, the individual components of VALETTE. Long-term studies in rats and mice with dienogest showed increased incidences of pituitary adenomas, fibroepithelial mammary tumours, stromal polyps of the uterus, and malignant lymphoma, at doses corresponding to exposure levels about 10 times that anticipated at the maximum recommended clinical dose, based on AUC. Similar tumours have been shown to develop with other estrogenic /progestogenic compounds. The tumours are thought to result from marked species differences in the optimal estrogen:progestogen ratio for reproductive function. Dienogest showed no tumour promotion activity in the rat liver foci assay at exposure levels corresponding to >100 times the estimated human exposure at the clinical dose, based on AUC.

Although long-term animal studies did not definitely indicate a tumourigenic potential for the clinical use of either dienogest or ethinylestradiol, it should be noted that the tumourigenic potential of a combination of ethinylestradiol and dienogest has not been specifically investigated. Also, it must be borne in mind that sex steroids can promote the growth of certain hormone-dependent tumours

## Effect on laboratory tests

The use of contraceptive steroids may influence the results of certain laboratory tests, including biochemical parameters of liver, thyroid, adrenal and renal function, plasma levels of carrier proteins, e.g. corticosteroid binding globulin and lipid/lipoprotein fractions, parameters of carbohydrate metabolism and parameters of coagulation and fibrinolysis. Changes generally remain within the normal laboratory range.

## INTERACTIONS WITH OTHER MEDICINES

Note: The prescribing information of concomitant medications should be consulted to identify potential interactions.

### Effect of other medicines on VALETTE

Interactions can occur with medicines that induce microsomal enzymes which can result in increased clearance of sex hormones and which may lead to breakthrough bleeding and/or contraceptive failure.

Enzyme induction can already be observed after a few days of treatment. Maximal enzyme induction is generally seen within a few weeks. After the cessation of drug therapy enzyme induction may be sustained for about 4 weeks.

Women prescribed any of these medicines should temporarily use a barrier method in addition to the COC, or choose another method of contraception. The barrier method should be used during the time of concomitant drug administration and for 28 days after their discontinuation. If the period during which the barrier method is used runs beyond the end of the white active tablets, the brown placebo tablets should be omitted and the next COC pack should be started with the white active tablet in the green section of the corresponding day.

- **Substances increasing the clearance of COCs (diminished efficacy of COCs by enzyme-induction), e.g.**

Phenytoin, barbiturates, primidone, carbamazepine, rifampicin, and possibly also oxcarbazepine, topiramate, felbamate, griseofulvin and products containing St. John's Wort.

- **Substances with variable effects on the clearance of COCs, e.g.**

When co-administered with COCs, many HIV/hepatitis C virus (HCV) protease inhibitors and non-nucleoside reverse transcriptase inhibitors can increase or decrease plasma concentrations of estrogen or progestin. These changes may be clinically relevant in some cases.

- **Substances decreasing the clearance of COCs (enzyme inhibitors)**

Dienogest is a substrate of cytochrome P450 (CYP) 3A4.

Strong and moderate CYP 3A4 inhibitors like azole antifungals (e.g. ketoconazole, itraconazole, voriconazole, fluconazole), cimetidine, verapamil, macrolides (e.g. clarithromycin, erythromycin), diltiazem, antidepressants and grapefruit juice may increase plasma levels of the estrogen or progestogen or both.

Etoricoxib doses of 60 to 120 mg/day have been shown to increase plasma concentrations of ethinylestradiol by 1.4 to 1.6-fold respectively, when taken concomitantly with a COC containing 35 µg ethinylestradiol.

### Effects of VALETTE on other medication

Oral contraceptives may affect the metabolism of certain other medicines. Accordingly, plasma and tissue concentrations may increase (e.g. cyclosporin) or decrease (e.g. lamotrigine).

In clinical studies, administration of a hormonal contraceptive containing ethinylestradiol lead to no, or a weak increase in CYP3A4 substrates (e.g. midazolam) and a weak (e.g. theophylline) to moderate (e.g. melatonin, tizanidine) increase of CYP1A2 substrates.

### Pharmacodynamic interactions

Co-administration of ethinylestradiol-containing medicinal products with direct-acting antiviral (DAA) medicinal products containing ombitasvir, paritaprevir or dasabuvir and combinations of these has been shown to be associated with increases in alanine aminotransferase (ALT) levels to greater than 20 times the upper limit of normal in healthy female subjects and HCV infected women (see CONTRAINDICATIONS).

### ADVERSE EFFECTS

Various adverse effects have been associated with oral contraceptive use. The most serious adverse effects associated with the use of oral contraceptives are dealt with under PRECAUTIONS.

In the event of aggravation, exacerbation or first appearance of any of these conditions or risk factors, the woman should contact her doctor. The doctor should then decide on whether its use should be discontinued.

### Clinical trial data

The incidence of adverse events was derived from the Phase III contraception study involving 2,290 women for a total of 28,183 cycles. The text below lists the adverse events (whether attributable to the medication or not) reported at a frequency of  $\geq 1\%$  of the events occurred in this study.

ADVERSE EFFECT	% OF ADVERSE EFFECT
<b>Skin and appendage disorders</b>	
Acne	3.90
Alopecia	1.39
<b>Peripheral nervous system</b>	
Headache	8.1
Migraine	1.49
<b>Psychiatric system</b>	
Depressive moods	1.2

<b>ADVERSE EFFECT</b>	<b>% OF ADVERSE EFFECT</b>
<b>Gastrointestinal system disorders</b>	
Nausea /vomiting	2.1
Enteritis	1.39
<b>Cardiovascular disorders</b>	
Hypertension	1.11
Hypotension	1.95
<b>Respiratory system disorders</b>	
Bronchitis	4.36
Pharyngitis	5.48
Rhinitis	1.86
Sinusitis	1.76
<b>Urinary system disorders</b>	
Cystitis	2.32
Urinary tract infection	1.49
<b>Reproductive system</b>	
Breast tenderness	5.4
Dysmenorrhoea	1.02
Leukorrhoea	1.21
Salpingitis	1.58
Vaginitis	3.62
<b>Neoplasm</b>	
Ovarian cyst	1.39
<b>Body as a whole</b>	
Reduced libido	1.1
Allergy	2.51
Back pain	1.21
Influenza-like symptoms	16.16
<b>Resistance mechanism disorders</b>	
Fungal infection	2.32
Moniliasis	1.95

In acne Study 28501, which included patients with mild to moderate acne, the frequency of adverse events in the VALETTE group (n = 525) compared to the placebo group (n = 264) was as shown in the following table (for events affecting  $\geq 1\%$  of the VALETTE patients, i.e., at least 6 of 525), whether attributable to the medication or not.



ADVERSE REACTION	VALETTE % OF PATIENTS	PLACEBO % OF PATIENTS
<b>Gastrointestinal disorders</b>		
Nausea	4.2%	2.7%
Vomiting	3.0%	1.9%
Diarrhoea	1.3%	2.3%
<b>Infections and infestations</b>		
Influenza	2.1%	1.1%
Nasopharyngitis	1.7%	3.0%
Respiratory tract infection viral	1.5%	1.1%
<b>Nervous system disorders</b>		
Headache	5.3%	5.3%
<b>Reproductive system and breast disorders</b>		
Breast pain	2.1%	0.0%
Metrorrhagia	2.1%	0.0%
Breast tenderness	1.5%	0.8%

Other adverse drug reactions reported in clinical trials with VALETTE, as oral contraceptive and in the treatment of mild to moderate acne in women who seek oral contraception, includes:

**Infections and infestations:** vulvovaginitis, vaginal candidiasis or other fungal vulvovaginal infections, salpingo-oophoritis, mastitis, cervicitis, candidiasis, oral herpes, upper respiratory infections, viral infection

**Neoplasms benign, malignant and unspecified (incl. cysts and polyps):** uterine leiomyoma, lipoma of breast

**Blood and lymphatic system disorders:** anaemia

**Endocrine disorders:** virilism

**Metabolism and nutrition disorders:** increased appetite, anorexia

**Psychiatric disorders:** depressed mood, mental disorder, insomnia, sleep disorder, aggression, libido decreased, libido increased

**Nervous system disorders:** dizziness, ischaemic stroke, cerebrovascular disorder, dystonia

**Eye disorders:** dry eye, eye irritation, oscillopsia, visual impairment

**Ear and labyrinth disorders:** sudden hearing loss, tinnitus, vertigo, hearing impaired

**Cardiac disorders:** cardiovascular disorder, tachycardia (including hear rate increased)

**Vascular disorders:** venous and arterial thromboembolic events, thrombophlebitis, diastolic hypertension, orthostatic circulatory dysregulation, hot flush, varicose veins, vein disorder, vein pain

**Respiratory thoracic and mediastinal disorders:** hyperventilation

**Gastrointestinal disorders:** gastritis, dyspepsia

**Skin and subcutaneous tissue disorders:** rash (including rash macular), pruritus (including pruritus generalised), dermatitis allergic, dermatitis atopic/neurodermatitis, psoriasis, hyperhidrosis, pigmentation disorder, hyperpigmentation, seborrhoea, dandruff, hirsutism, skin disorder, skin reaction, peau d'orange, spider naevus

**Musculoskeletal and connective tissue disorders:** musculoskeletal discomfort, myalgia

**Reproductive system and breast disorders:** abnormal withdrawal bleeding (including menorrhagia, hypomenorrhoea, oligomenorrhoea, and amenorrhoea), breast enlargement (including breast engorgement and breast swelling), breast oedema, genital/vaginal discharge, pelvic pain, cervical dysplasia, adnexa uteri cyst, adnexa uteri pain, breast cyst, fibrocystic breast disease, dyspareunia

**General disorders and administration site conditions:** fatigue (including asthenia and malaise), chest pain, oedema peripheral, inflammation, pyrexia, irritability

**Investigations:** weight changes (including weight increase, decrease and fluctuation), blood triglycerides increased, hypercholesterolaemia

**Congenital familial and genetic disorders:** manifestation of asymptomatic accessory breast

## **Post-marketing data**

The following undesirable effects have been reported in users of VALETTE or other COCs and the association has been neither confirmed nor refuted.

**Cardiovascular:** deep venous thrombosis, pulmonary embolism, cerebral infarction, thrombosis, migraine, stroke, occlusion retinal artery, hepatic haemangioma, superficial thrombophlebitis, hypertension, peripheral vascular disease

**Genital tract:** intermenstrual bleeding (consisting of vaginal haemorrhage and metrorrhagia), menstrual disorders, vaginal mycosis

**Digestive:** nausea, vomiting, diarrhoea, cholelithiasis, liver neoplasm, fatty liver, pancreatitis, hepatitis, hepatic cyst, decreased cholinesterase, gingivitis and abdominal pain (including upper and lower abdominal pain, abdominal discomfort/distention).

**Nervous system:** depression, mood altered, headache, migraine, galactorrhoea, paresthesia and changes in libido

**Musculoskeletal:** articular swelling

**Respiratory tract:** voice alteration, dyspnoea, asthma

**Skin:** dermatitis, rash, urticaria, erythema nodosum, erythema multiforme, atopic eczema (exacerbation), papulous exanthema, chloasma

**Eyes:** contact lens intolerance, blurred vision

**Metabolic:** hypertriglyceridemia, oedema, change in weight, fluid retention

**Haemic and lymphatic:** haemorrhagic purpura, leucopenia

**Body as a Whole:** anaphylactic reaction, pain in extremities

**Breast disorders:** breast pain (including breast discomfort and breast tenderness), hypertrophy breast and breast discharge

**Immune system disorders:** hypersensitivity

**Special senses:** acute deafness

In women with hereditary angioedema exogenous estrogens may induce or exacerbate symptoms of angioedema.

## **DOSAGE AND ADMINISTRATION**

Combined oral contraceptives, when taken correctly, have a failure rate of approximately 1% per year. The failure rate may increase when pills are missed or taken incorrectly.

Tablets must be taken in the order directed on the package every day at about the same time with some liquid as needed. Tablet taking is continuous. One tablet is to be taken continuously for 28 consecutive days. Each subsequent pack is started the day after the last tablet of the previous pack. Withdrawal bleeding usually starts on Day 2-3 after starting the brown placebo tablets (last row) and may not have finished before the next pack is started.

### **How to start VALETTE**

- **No preceding hormonal contraceptive use (in the past month)**

Tablet-taking has to start on Day 1 of the woman's natural cycle (i.e. the first day of her menstrual bleeding). The women should be instructed to take a white active tablet from the green section of the pack, corresponding to that day of the week. If VALETTE is started as described above; there is no need to employ an additional barrier method of contraception during the first cycle.

Starting on Day 2-5 of menstrual bleeding is allowed, but during the first cycle a barrier method is recommended in addition for the first 7 days of tablet-taking.

- **Changing from a combined hormonal contraceptive (COC) or vaginal ring**

The woman should start with VALETTE preferably on the day after the last active tablet of her previous COC, but at the latest on the day following the usual tablet-free or placebo tablet interval of her previous COC.

In case a vaginal ring has been used, the woman should start taking VALETTE preferably on the day of removal of the ring, but at the latest when the next application would have been due. VALETTE should be started by taking a white active tablet from the green section of the pack.

- **Changing from a progestogen-only method (minipill, injection, implant) or from a progestogen-releasing intrauterine system (IUS)**

The woman may switch from the minipill on any day, from an implant or the IUS on the day of its removal, or from an injectable when the next injection would be due, but in all of these cases she should be advised to additionally use a barrier method for the first 7 days of tablet-taking.

- **Following first-trimester abortion**

The woman may start immediately. When doing so, she need not take additional contraceptive measures.

- **Following delivery or second-trimester abortion**

For breastfeeding women see Use in lactation.

Women should be advised to start on Day 21 to 28 after delivery or second-trimester abortion. When starting later, the woman should be advised to additionally use a barrier method for the first 7 days of tablet-taking. However, if intercourse has already occurred, pregnancy should be excluded before the actual start of COC use or the woman has to wait for her first menstrual period.

### **Management of missed tablets**

Missed pills from the last row of the blister are placebo tablets and thus can be disregarded. However they should be discarded to avoid unintentionally prolonging the placebo tablet phase. The following advice only refers to missed white active tablets (rows 1-3 of the blister).

If the woman is **less than 12 hours** late in taking any tablet, contraceptive protection is not reduced. The woman should take the tablet as soon as she remembers and should take further tablets at the usual time.

If she is **more than 12 hours** late in taking any tablet, contraceptive protection may be reduced. The management of missed tablets can be guided by the following two basic rules:

1. Tablet-taking must never be discontinued for longer than 7 days.
2. 7 days of uninterrupted tablet-taking are required to attain adequate suppression of the hypothalamic-pituitary-ovarian-axis.

The following advice can be given in daily practice:

#### Week 1

The woman should take the last missed tablet as soon as she remembers, even if this means taking two tablets at the same time. She then continues to take tablets at her usual time. In addition, a barrier method such as a condom should be used for the next 7 days. If intercourse took place in the preceding 7 days, the possibility of a pregnancy should be considered. The more tablets are missed and the closer they are to the placebo tablet phase the higher the risk of a pregnancy.

## Week 2

The woman should take the last missed tablet as soon as she remembers, even if this means taking two tablets at the same time. She then continues to take tablets at her usual time. Provided that the woman has taken her tablets correctly in the 7 days preceding the first missed tablet, there is no need to use extra contraceptive precautions. However, if this is not the case, or if she missed more than 1 tablet, the woman should be advised to use extra precautions for 7 days.

## Week 3

The risk of reduced reliability is imminent because of the forthcoming placebo tablet phase. However, by adjusting the tablet-intake schedule, reduced contraceptive protection can still be prevented. By adhering to either of the following two options, there is therefore no need to use extra contraceptive precautions, provided that in the 7 days preceding the first missed tablet the woman has taken all tablets correctly. If this is not the case, the woman should be advised to follow the first of these two options and to use extra precautions for the next 7 days as well.

1. The woman should take the last missed tablet as soon as she remembers, even if this means taking two tablets at the same time. She then continues to take tablets at her usual time until all the active tablets are used up. The 7 tablets from the last row (placebo tablets) must be discarded. The next pack must be started right away. The woman is unlikely to have a withdrawal bleed until the end of the active tablets of the second pack, but she may experience spotting or breakthrough bleeding on tablet-taking days.
2. The woman may also be advised to discontinue tablet-taking from the current pack. She should then have a tablet-free interval of up to 7 days, including the days she missed tablets, and subsequently continue with the next pack.

If the woman missed tablets and subsequently has no withdrawal bleed in the placebo tablet interval, the possibility of a pregnancy should be considered.

## **Advice in case of gastrointestinal disturbances**

In case of severe gastrointestinal disturbances, absorption may not be complete and additional contraceptive measures should be taken.

If vomiting occurs within 3-4 hours after tablet-taking, absorption may not be complete. In such an event, the advice concerning missed tablets (see above) is applicable. If the woman does not want to change her normal tablet-taking schedule, she has to take the extra tablet(s) needed from another pack.

## **How to delay a period**

To delay a period the woman should continue with another pack of VALETTE without taking the brown placebo tablets from her current pack. The extension can be carried on for as long as wished until the end of the active tablets in the second pack. During the extension the woman may experience breakthrough-bleeding or spotting. Regular intake of VALETTE is then resumed with the next pack.

## **OVERDOSAGE**

There have been no reports of serious deleterious effects from overdose. On the basis of general experience with COCs, symptoms that may occur in case of overdose of active

tablets are: nausea, vomiting and withdrawal bleeding. There are no antidotes and further treatment should be symptomatic. The later may occur in girls before their menarche, if they have accidentally taken the product.

In cases of overdose, it is advisable to contact the Poisons Information Centre (131126) for recommendations on the management and treatment of overdose.

## **PRESENTATION AND STORAGE CONDITIONS**

VALETTE tablets are contained in blister packs. Each blister contains 21 white active tablets containing dienogest 2 mg and ethinylestradiol 30 µg, followed by 7 brown placebo tablets.

Carton containing blister packs of 1 x 28, 2 x 28, 3 x 28 or 4 x 28 tablets. Not all pack sizes may be marketed.

Store below 30°C.

## **NAME AND ADDRESS OF THE SPONSOR**

Bayer Australia Ltd  
ABN 22 000 138 714  
875 Pacific Highway  
Pymble NSW 2073

## **POISON SCHEDULE OF THE MEDICINE**

S4

## **DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (ARTG)**

2 March 2006

## **DATE OF MOST RECENT AMENDMENT**

11 January 2018

## **REFERENCES:**

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- 1 Dinger JC, Heinemann LA, Kuhl-Habich D. The safety of a drospirenone-containing oral contraceptive: final results from the European Active Surveillance study on Oral Contraceptives based on 142,475 women-years of observation. *Contracept* 2007; 75:344-54.
  - 2 Heit JA, Kobbervig CE, James AH et al. Trends in the incidence of venous thromboembolism during pregnancy or postpartum: a 30 year population based study. *Ann Intern Med.* 2005; 143:697-706.